

Peripheral circulatory adaptations to pump failure of the heart

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Impairment of ventricular performance is the initial step in the development of heart failure, but the symptoms and the reduced exercise capacity cannot solely be explained by left ventricular dysfunction. The degree of ventricular dysfunction in congestive heart failure (CHF) does not correlate with its severity—that is, indices of left ventricular dysfunction do not predict or correlate closely with the functional state of patients with CHF as assessed by exercise tests.¹ Although right ventricular dysfunction has been linked to the severity of symptoms and exercise intolerance, right ventricular failure seems to be a secondary problem in most cases of clinical systolic heart failure. There is evidence that prognosis is associated with the degree of left ventricular dysfunction, extent of myocardial loss, and cardiac dimensions. Clinical symptoms of heart failure usually emerge with the activation of neurohumoral systems, in particular the sympathetic system and the renin-angiotensin system. The study of left ventricular dysfunction (SOLVD) trial confirmed that increases of plasma atrial natriuretic peptide and noradrenalin occur early in the disease and plasma renin activity increases with symptoms.² Although numerous factors are likely to be involved in the development of symptoms, the decrease in renal perfusion may activate the renin-angiotensin system. Experimental data suggest that this alteration of renal haemodynamics emerges early in the course of heart failure. Sodium retention may also emerge early and compensate for impaired left ventricular dysfunction by increasing the preload. One important clinical symptom in chronic heart failure is early fatigue during physical activity, which has

been linked to impaired perfusion of skeletal muscle during exercise. In patients with chronic heart failure, the increase during exercise in blood flow to working muscle and the oxygen consumption are less than those of normal people, whereas plasma lactate concentrations are increased for each given workload.³ Most of the reduction in maximal blood flow during exercise occurs in oxidative working muscle.⁴ This impairment of metabolic vasodilatory capacity within skeletal muscle during exercise has often been attributed to excessive sympathetically mediated vasoconstriction, activation of the plasma renin-angiotensin system and more recently to increased concentrations of endothelin (fig 1).⁵ It seems that endothelin concentrations play an important part in the pulmonary circulation⁶ but its pathophysiological relevance in the systemic circulation remains uncertain. Although these neurohumoral factors exert potent systemic and regional vasoconstriction, they do not completely explain the impairment of vasodilating capacity within skeletal muscle in patients with chronic heart failure. Impaired metabolic vasodilatation during exercise cannot be restored by α blockade with phentolamine.^{7,8} Similarly, a dose of angiotensin converting enzyme (ACE) inhibitor does not restore metabolic vasodilatation to normal despite substantial reductions of plasma angiotensin II and noradrenaline (norepinephrine) concentrations.⁹ This indicates that blockade of the plasma renin angiotensin system by ACE inhibitors does not interfere with blood flow to working muscle during exercise in patients with CHF.^{9,10} After treatment with an ACE inhibitor for several months, a notable increase in femoral blood flow during exercise is found and is accompanied by an improved peak oxygen consumption.⁹ Thus, long-term ACE inhibitor treatment reversed the inability of peripheral vessels to dilate. This is consistent with previous findings that the full beneficial effect of ACE inhibitor treatment in large scale trials emerges slowly with time.¹¹ Similarly, peripheral perfusion and skeletal muscle function take weeks or months to return to normal after cardiac transplantation.

What are the mechanisms for the delayed beneficial effects of ACE inhibitors or cardiac transplantation? It is important to note that exercise tolerance in patients with heart failure is not determined solely by central haemodynamics. One possible explanation could be that the delayed effect of ACE inhibitors may be partly due to its interference with the

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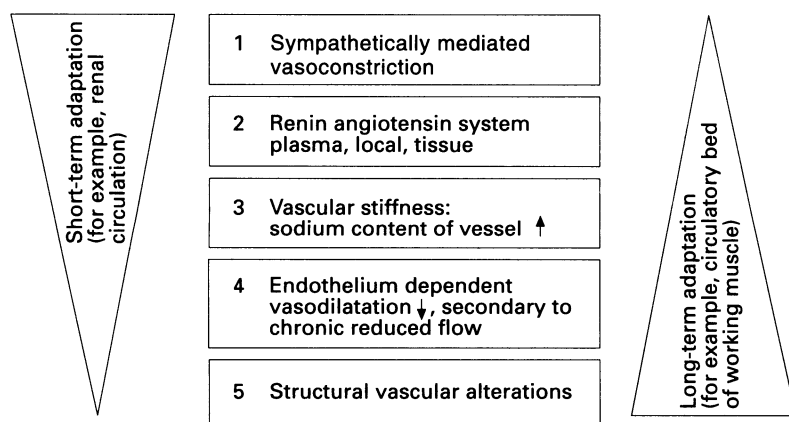


Figure 1 Regional vascular compensatory vasoconstrictor mechanisms in congestive heart failure.

vascular tissue renin-angiotensin system, which reverses chronic structural alteration of the vessel. Experimental evidence indicates that angiotensin II induces hypertrophy of cultured rat aortic smooth muscle cells.¹² Angiotensin II, endothelin, and noradrenaline seem to be involved in the activation of proto-oncogenes.¹³ This suggests that angiotensin II may be involved in the proliferative process of tissues during growth (endogenous growth factor). Recent findings indicate that ACE inhibition can reverse structural vascular alteration in a rat model of hypertension¹⁴ to a greater extent than can other antihypertensive drugs.¹⁵

Unfortunately, experimental and clinical studies investigating structural alterations in chronic heart failure are scarce and contradictory. Although some studies have indicated that structural abnormalities might occur at the level of the resistance vessel¹⁶ others did not show such alterations.¹⁷ The clinical studies usually have been confined to skin resistance vessels and may not be representative of skeletal muscle resistance vessels. Small biopsies of skeletal muscle often allow examination of only very small arterioles (<50 μm), which may not play the main part in regulating blood flow. This seems also to be true of resistance vessels that range from 80–200 μm . Other potential mechanisms involved in the impairment of metabolic peripheral dilatation in chronic heart failure include a vascular stiffness component owing to the increased vascular sodium content, which can be partly reduced with diuretic treatment in decompensated heart failure.¹⁸ Although it remains controversial whether structural changes occur in the microcirculation of skeletal muscle, flow dependent dilatation, and dilatation of large conduit vessels induced by glyceryl trinitrate are impaired in patients with heart failure indicating that these patients have impaired relaxation of vascular smooth muscle and have impaired elastic properties of the large conduit vessels.¹⁹ This may have functional consequences through a negative feedback on the pumping performance of the left ventricle.

Endothelial dysfunction

The pivotal role of the endothelium derived relaxing factor on vascular tone is now recognised. Nitric oxide, which accounts for most of the biological activity of endothelium derived relaxing factor, is continuously released from the endothelium, and this basal release of nitric oxide provides a constant counteracting force to vasoconstrictor substances such as noradrenaline or angiotensin II. Secondly, endothelium derived relaxing factor can be released from the endothelium upon stimulation—that is, by bradykinin or ADP. Several pathophysiological conditions such as hypercholesterolaemia or hypertension are associated with dysfunctional endothelium—that is, either the basal or stimulated release of endothelium derived relaxing factor is altered. Recent data from our labora-

tory and others showed that endothelium dependent relaxation of the microcirculation of skeletal muscle in response to acetylcholine is impaired in chronic heart failure whereas the vasodilating effect of glyceryl trinitrate is preserved.^{20–22} Although the functional importance of this finding remains unclear, it seems likely that endothelial dysfunction in the peripheral circulation is involved in the impairment of both reactive hyperaemia and increase in blood flow in heart failure. Studies on the coronary circulation have shown that inhibition of the synthesis of nitric oxide reduces the total reactive hyperaemia.

The basal release of nitric oxide, which accounts for the biological activity of endothelium derived relaxing factor,²³ has been shown to contribute to the control of regional blood flow in humans by the use of N-monomethyl-L-arginine (L-NMMA), a selective inhibitor of nitric oxide from L-arginine.²⁴ In the absence of notable vasoconstriction of conduit vessels, changes in blood flow indicate the response of resistance vessels. To identify the endothelium dependent vasomotor response of large forearm conduit *v* small resistance vessels we used a novel ultrasound device to determine forearm arterial diameter accurately.^{25,26} Simultaneously, blood flow velocity was recorded by a Doppler velocity device in the same vessel. By this method, the effects of intra-arterial infusion of acetylcholine, L-NMMA, and glyceryl trinitrate on forearm conduit and resistance vessels were examined in patients with chronic CHF and age matched healthy volunteers. Although the blood flow response to acetylcholine was blunted in patients with CHF, the decrease in flow induced by L-NMMA was enhanced and the response to glyceryl trinitrate was preserved.²¹ As L-NMMA inhibits the basal release of nitric oxide, an exaggerated vasoconstrictor response in patients with heart failure (compared with controls) is consistent with the notion that the basal release of nitric oxide is increased in the peripheral circulation of patients with heart failure. Thus, endothelium dependent dilatation of forearm resistance vessels is impaired in patients with CHF, suggesting a reduced stimulated release of nitric oxide in response to acetylcholine. The basal release of nitric oxide seems to be enhanced, however, in a compensatory manner. As the dilator response to both acetylcholine and glyceryl trinitrate involves the activation of the guanylate cyclase system (or a non-specific effect of opposing constrictor forces) a generalised defect within the guanylate cyclase system cannot account for this finding. Thus in patients with heart failure, the stimulated release of endothelium derived relaxing factor seems to be attenuated resulting in an impaired endothelium dependent relaxation of resistance vessels. This does not establish a general impairment of endothelial function or specifically an impairment of the basal release of nitric oxide synthesised from L-arginine. Indeed, blood flow after a high dose of L-NMMA was even more reduced in patients with CHF than in normal people.

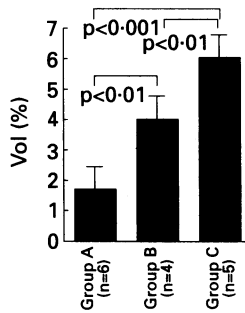


Figure 2 Volume density of mitochondria with cytochrome c oxidase positive cristae. Group A, patients with severe heart failure; group B, patients with moderate heart failure; group C, normal controls.

Thus it seems that the stimulated and basal release of nitric oxide are dissociated in patients with heart failure. The basal release of nitric oxide seems to be preserved or may even be enhanced in the peripheral circulation whereas the stimulated endothelial dependent dilatation exerted by acetylcholine is blunted. The finding that forearm blood flow was substantially reduced with L-NMMA without important changes in the diameters of large conductance vessels in normal people suggests a preferential release or activity of nitric oxide in forearm resistance vessels compared with large conductance vessels in humans. Thus the basal release of nitric oxide seems to play an important part in modulating tissue perfusion in distal resistance vessels in the forearm in heart failure but may be negligible in conduit vessels, or other factors may override this effect on vasomotor tone in large arteries.

Experimental evidence shows that long-term treatment with ACE inhibitors and physical training improve endothelial dysfunction in experimental heart failure.²⁷ Preliminary data indicate that training can improve endothelial function in patients with heart failure.²⁸ The beneficial effect of ACE inhibitors on endothelial function might be due to the inhibition of the breakdown of bradykinin, which is degraded by ACE.²⁹ Inhibition of the ACE mechanism may increase the local tissue concentrations of bradykinin, which in turn stimulates the release of nitric oxide (which accounts for the biological activity of the endothelium derived relaxing factor) and vasodilating prostaglandins.^{29, 30}

Intrinsic alterations of skeletal muscle in chronic heart failure

Although acute doses of vasodilators or positive inotropes may improve blood flow to skeletal muscle during exercise, duration of exercise and maximal oxygen consumption do not increase immediately after these drugs are given.³¹ This indicates that oxygen uptake within skeletal muscle during exercise cannot be improved during short-term intervention in patients with chronic heart failure even when oxygen delivery is enhanced. This finding suggests that blood flow is shunted away from active muscle or that there are intrinsic alterations of skeletal muscle in chronic heart failure, or both. We have noted previously that there might be a shift from oxidative skeletal muscle to activation of more glycolytic working muscle fibres⁴ again indicating a change in the properties of the skeletal muscle itself. Muscle biopsies taken from patients with chronic heart failure showed moderate atrophy (reduced muscle mass) and biochemical alterations including a shift in the distribution of fibre type in skeletal muscle.^{32, 33} Ultrastructural analysis of skeletal muscle biopsy specimens has shown a reduced oxidative capacity of the muscle as indicated by a reduced volume, density, and reduced surface area of the cristae of mitochondria.³⁴

Cytochrome c oxidase staining of the ultrastructural and biochemical measurement of citrate synthase showed a significantly reduced concentration of the oxidative enzymes (fig 2),^{34, 35} which suggests that the oxidative capacity of skeletal muscle is diminished in severe chronic heart failure. In fact, a close relation has been found between the oxidative capacity of working muscle, as assessed by cytochrome c oxidase or cristae surface density of mitochondria within the skeletal muscle and the peak oxygen consumption during exercise.^{34, 36} Thus exercise capacity seems to be partly determined by the condition of the working muscle.³⁷ The pattern obtained by nuclear magnetic resonance spectroscopy showed abnormal metabolism of skeletal muscle, which supported the ultrastructural and biochemical findings.³⁸ With nuclear magnetic resonance spectroscopy, it was shown that the intracellular pH values during exercise are much lower for a given workload in patients with severe heart failure. Moreover, during exercise, the concentrations of plasma inorganic phosphate and phosphocreatinine decreased much faster in patients with heart failure than in normal people.^{38, 39}

Potential underlying mechanisms of peripheral adaptations

Many experimental and human studies have shown that exercise training induces important adaptations in skeletal muscle.⁴⁰ These include increases in capillary supply, muscle mass, mitochondrial content including increased activity of oxidative enzymes, and a shift in the distribution of fibre types—that is, a higher percentage of type I and IIA muscle fibres that possess a higher oxidative capacity than type IIB fibres. This adaptation of skeletal muscle to training results in an increased respiratory capacity of the muscle fibres accompanied by metabolic consequences, such as slower use of muscle glycogen, greater reliance on fat oxidation, and lower lactate production during exercise of a given intensity.⁴⁰ In contrast, during prolonged immobilisation, oxidative enzymes of skeletal muscle, muscle mass, and capillary density all decrease below baseline values.^{41–43} As patients with chronic heart failure usually restrict their physical activity, in part based on their physicians' advice, the hypothesis has been put forward that a deconditioning effect occurs in their skeletal muscle.⁴⁴ Consistent with this concept, bicycle training in patients with chronic heart failure has been shown to improve exercise tolerance by peripheral mechanisms—for example, by delaying the onset of anaerobic metabolism.⁴⁵ Training induced improvement of peripheral muscle metabolism seems to be independent of systemic adaptations. Both in normal people and patients with heart failure, an exercise programme restricted to small muscle groups (such as forearm muscles) improves the metabolic state of skeletal muscle without altering cardiac performance.⁴⁶

Although these findings suggest that the alterations in skeletal muscle of patients with chronic heart failure are due to deconditioning, other potential factors should not be dismissed. Mancini *et al* suggest that decreased caloric and protein intake may be a main contributor to skeletal muscle atrophy.³² It would be interesting to see whether or not there is a relation between indices of muscle atrophy and caloric intake. Depressed caloric intake may be an important factor in certain subsets of patients, particularly patients with alcoholic cardiomyopathy. Given the frequent lack of signs of malnutrition, however, other factors are likely to be involved in the development of muscle abnormalities. These factors may include increased free radical activity,⁴⁷ increased sympathetic tone, or monocyte activation associated with increased plasma concentrations of tumour necrosis factor.^{48,49} This monocyte activation, possibly linked to a stimulated renin-angiotensin system in severe heart failure,⁴⁹ may cause endothelial dysfunction⁵⁰ and adversely affect muscle metabolism and function.⁵¹ Indeed, there is evidence that in patients with cardiac cachexia the net negative protein balance across leg tissue is associated with an increased rate of myofibrillar protein breakdown.⁵² Endothelial dysfunction, which has been shown to emerge in patients with heart failure,²¹ may further compromise skeletal muscle function by affecting its blood flow. Long-term ACE inhibition improves blood flow to skeletal muscles and oxygen extraction during exercise.⁹ Also, preliminary data indicate that ACE inhibitors partially reverse ultrastructural abnormalities of skeletal muscle in patients with heart failure.³⁴ Experimental evidence suggests that long-term ACE inhibitor treatment reduces vascular infiltration by monocytes and macrophages and restores endothelial function.^{53,54} Some of these findings support the view that alterations of skeletal muscle in heart failure are, after all, the consequence of impaired cardiac function. It has been speculated, however, that a generalised myopathy may occur in a subset of patients with dilated cardiomyopathy.^{55,56} Dunnigan *et al* found that young patients with cardiomyopathy who developed either ventricular tachycardia or heart failure have histological abnormalities of skeletal and cardiac muscle, in particular, atrophy of type II skeletal muscle fibres.⁵⁵ Caforio *et al* reported histological alterations characterised by selective atrophy of type I fibres, that are similar to those found in congenital and idiopathic myopathies and are unrelated to cardiac functional New York Heart Association classes.⁵⁶ Thus, common underlying factors—for example, genetic or autoimmune disorders—that affect both cardiac and skeletal muscle may be operating in a subset of patients with dilated or hypertrophic cardiomyopathy. These divergent morphological findings are based on qualitative histological and ultrastructural analysis of upper arm skeletal muscle in a limited number of young patients without clinically overt myopathy.^{55,56} In contrast, in most reports evaluating weight

bearing calf muscle, the abnormalities were similar in patients with heart failure whether due to coronary artery disease or to dilated cardiomyopathy, suggesting that in most cases the reduced oxidative capacity of skeletal muscle is related to the state of heart failure and its severity.

The impact of impaired blood flow during exercise on these skeletal muscle alterations remains unclear. Subsequent studies with nuclear magnetic resonance spectroscopy as well as skeletal muscle function tests in patients with chronic heart failure showed that these abnormalities, under ischaemic conditions, were unrelated to different rates of blood flow to the working muscle during exercise.^{57–59} This does not exclude the fact that repeated episodes of reduced blood flow within skeletal muscle may be involved in the development of skeletal muscle alterations, despite the fact that these alterations, once developed, can be shown regardless of measured flow during the assessment of muscle function⁵⁹ or metabolism.^{57,58}

The alterations of the peripheral circulation in chronic heart failure are similar to those found after prolonged physical inactivity. In contrast, opposite changes can be found after intense training—that is, in athletes. Several small studies have documented that a training programme can reverse at least some of the adverse peripheral changes.^{45,60} Based on the theoretical considerations, physical training has a great potential to improve the clinical state of patients with heart failure. Before widespread recommendations can be made the safety of training in patients with heart failure needs to be shown in large populations of patients. In particular, the impact of physical training on cardiac function needs to be tested vigorously. Although some animal studies by Scheuer *et al* indicate that training may improve the myocardial phenotype and improve cardiac performance, these studies were almost exclusively performed in rats.^{61,62} The myocardium of rats has specific properties distinct from the human myocardium, and more importantly, coronary artery disease in humans usually complicates matters. In the end, there may be an interaction between cardiac performance during exercise and the progressive perfusion deficit in skeletal muscle during exercise. It is now established that the force frequency relation is substantially altered in human heart failure—that is, twitch tension of the failing heart decreases with increased heart rate (peak twitch tension 50–70 beats/min), whereas the peak twitch tension in the normal myocardium is 130 to 140 beats/min. Thus the increase in heart rate in normal people during exercise is associated with increased cardiac output but this myocardial inotropic reserve cannot be recruited in the failing heart and may be involved in the impaired perfusion during exercise. Recent data from our laboratory indicate that the impaired force frequency relation during exercise is related to an altered cardiac phenotype of the expression of the sarcoplasmic reticulum ATPase. Future

studies, by integrating cardiac, pulmonary, reflex, vascular, and skeletal muscular aspects should be able to delineate the composite alterations responsible for the clinical syndrome of heart failure.

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